

Research Report

Effects of stimulus rate on signal response during functional magnetic resonance imaging of auditory cortex

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Abstract

Functional magnetic resonance imaging (fMRI) detects focal MRI signal changes in brain tissue that are believed to result from changes in neuronal activity. We describe the dependence of this response in auditory cortex on the rate of presentation of simple speech stimuli. Speech syllables were presented to five normal subjects at rates ranging from 0.17 to 2.5 Hz, while the subjects performed a phoneme discrimination task. Regions studied with fMRI during this task included the lateral aspect of both temporal lobes. All subjects showed bilateral superior temporal lobe MRI signal increases that were coincident with stimulus presentation and performance of the task. The magnitude of this response increased in a monotonic, non-linear manner with increasing stimulus rate. This rate-response relationship was nearly identical in right and left hemispheres. The relationship may reflect metabolic activity integrated over time and subject to non-linear characteristics of neuronal recovery or blood flow regulation. The dependence of response magnitude on stimulation rate supports the hypothesis that the fMRI phenomenon indirectly reflects neuronal metabolic activity. The measures provided here should assist in the design of optimal activation strategies for the human auditory cortex.

Key words: Cerebral blood flow; Cerebral metabolism; Auditory cortex; Functional imaging; Speech perception; Temporal lobe

1. Introduction

Functional magnetic resonance imaging (fMRI) is a new technique for detecting focal physical changes associated with brain activity. MRI signal changes observed with the technique are believed to reflect increases in tissue oxygenation resulting from neuronal activity [2,10]. Investigations to date have demonstrated discrete areas of signal change in response to complex visual, motor, and auditory stimuli [2,3,10,18]. Much of this work has proceeded with little information about the effects on response magnitude of such simple stimulus variables as rate, intensity, and duration. Such factors have been shown in animal studies to affect regional glucose utilization in peripheral and central sensory pathways [12,22,27]. Rate has been shown to be a significant variable determining regional cerebral blood flow in humans as determined by positron emis-

sion tomography (PET) [6,16]. One fMRI study demonstrated a relation between stimulus rate and activation in the visual cortex, closely paralleling that observed by PET [10]. In developing fMRI as an experimental and clinical tool, it will be essential to quantify the impact of such stimulus variables and to measure their interactions with complex phenomena such as attention, sequencing complexity, and linguistic content. Identification of physical variables determining the magnitude of signal change could also contribute to an understanding of the fMRI response and its relation to underlying neuronal events.

The following study measured fMRI responses in auditory cortex during a phoneme discrimination task in which the rate of stimulus presentation was varied systematically across trials. Our previous studies demonstrated consistent, bilateral superior temporal gyrus (STG) responses during passive exposure to relatively long phoneme clusters [3,17]. The present work incorporated stimuli of shorter duration (consonant-vowel syllables) permitting faster and more varied pre-

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Table 1
Subjects

Subject	Sex	Age	LQ
1	F	33	100
2	M	29	92
3	M	30	89
4	F	22	71
5	M	31	65

sentation rates. Pilot studies showed these stimuli to produce consistent cortical responses similar to those observed in prior studies.

2. Materials and methods

2.1. Subjects

Subjects were five healthy, right-handed individuals (2 women, 3 men), aged 22–33 years, with no history of neurologic or auditory symptoms. Individual data, including Edinburgh Handedness Inventory laterality quotients [14], are provided in Table 1. Subjects were recruited on a voluntary basis, gave written informed consent according to institutional guidelines, and were paid a small hourly stipend. All studies received prior approval by the institutional human research review committee.

2.2. Apparatus and scanning procedure

Imaging was performed on a GE 1.5 T Signa scanner using prototyping gradient and rf coils optimized for whole-volume echo-planar brain imaging in three axes [24,25]. A blipped gradient-echo echo-planar sequence was used for functional imaging, with acquisition of a 64×64 pixel image in 40 ms. The FOV was 24 cm and slice thickness 10 mm, yielding voxel dimensions of 3.75 mm×3.75 mm×10 mm. Symmetric lateral sagittal slices of the left and right hemispheres were obtained, centered at positions 13 mm medial to the most lateral point of the temporal lobe on each side. A functional imaging 'series' was comprised of 128 sequential images of each slice, alternating left and right-sided acquisitions, with an inter-scan temporal spacing, or TR, of 3 s for each side. Scanning also included acquisition of 5 mm 256×128 fast spin-echo anatomic reference images, located at the same position as the echo-planar images.

Subjects lay in the scanner with eyes closed and room lights dimmed. Digitally recorded auditory stimuli were played at precise intervals using a computer, amplified, and delivered binaurally to the subject via air conduction through a pair of plastic tubes 4 ft. in length. The air conduction system terminated in tightly-occlusive ear inserts allowing unimpeded conduction of the stimulus with good suppression of ambient scanner noise. Amplitude of the scanner pulse noise was measured at 95 dB SPL, with attenuation by the ear inserts of 15–20 dB. Mean stimulus amplitude, which remained constant across subjects, was 104 dB SPL.

Each 128-image echo-planar series consisted of multiple periods of 'baseline,' during which subjects heard only the ambient machine noise, alternating with periods of 'activation,' during which prepared auditory stimuli were delivered (Fig. 1). Each series began with 8 baseline images (24 s interval) allowing signal equilibrium to be reached and an initial baseline to be established, followed by 120 images during which activation alternated with baseline every 18 s (36 s/cycle, 12 images/cycle, 10 cycles). The total duration of each image series was 6 min 24 s. Five series (a total of 50 activation cycles) were obtained during a single 35 min session.

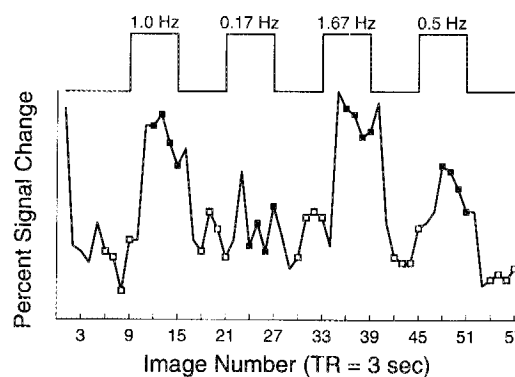


Fig. 1. Sample MRI signal data from a single pixel and illustration of the analysis method. The square wave at top indicates start and stop points of four activation cycles. Each activation is 18 s (6 images) in length and is followed by an equally long baseline period. The first activation used a 1.0 Hz frequency condition, began at image #9, and ended at image #15. The four images concluding each activation period (black squares) provided four signal measurements for each activation. These activation measurements were compared to a local baseline derived by averaging the four baseline values preceding and four values following the activation (white squares), and were expressed as a percent change from this baseline. Each image series included two activation cycles in each rate condition (four of which are shown here). Five image series were collected (total 50 activations), providing a total of ten activations, or 40 activation measurements, in each condition.

2.3. Auditory stimuli

Stimuli were 16-bit digital recordings of a male voice sampled at 44.1 kHz. These utterances included 90 distinct consonant-vowel (CV) syllables using the 18 sounds b, d, f, g, h, j, k, l, m, n, p, r, s, t, v, w, y, and z, in combination with the five vowels /æ/, /i/, /a/, /o/, and /u/. CV utterances were each edited to a duration of 400 ms and were presented in random order using five different rate conditions. Table 2 lists distinguishing features of these five conditions, including presentation rate, number of stimuli per 18-s activation cycle, aggregate stimulus duration per 18-s activation cycle, and inter-stimulus interval. Rate conditions remained constant for the duration of each 18-s activation cycle, but varied pseudo-randomly from cycle to cycle. Ten activation cycles were imaged in each condition.

To ensure that stimuli received subjects' attention, a phoneme discrimination task was performed during all conditions, in which subjects were required to respond to any occurrence of /b/ or /d/ by briefly lifting the index finger of their left hand. Target phonemes appeared 2–3 times during each 18-s activation period, regardless of the stimulus rate used. Finger responses were recorded by an investigator using a hand-held switch which produced an auditory signal in the control room. Stimuli and response signals were recorded in the

Table 2
Characteristics of the five stimulus conditions

	Presentation rate (Hz)	Stimuli per cycle	Total stimulus duration (s)	ISI (s)
1.	0.17	3	1.2	5.6
2.	0.50	9	3.6	1.6
3.	1.00	18	7.2	0.6
4.	1.67	30	12.0	0.2
5.	2.50	45	18.0	0.0

Table 3
Discrimination performance (d')

Rate (Hz)	S1	S2	S3	S4	S5	Mean
0.17	4.0	4.7	4.0	3.4	3.6	4.1
0.50	3.6	4.4	3.9	3.6	3.3	3.7
1.00	4.5	4.6	4.8	4.3	3.5	4.2
1.67	4.7	5.0	3.9	3.8	3.4	4.0
2.50	4.1	3.1	3.3	3.5	3.5	3.4

control room on auditory tape for off-line performance analysis. Subjects were briefly trained on the discrimination task prior to entering the scanner.

2.4. Data analysis

Performance data were analyzed separately for each subject. Detection indices (d') representing the difference between normalized 'noise' and 'signal+noise' distributions, were calculated from hit and false positive ratios in each of the five conditions [7].

Pixels showing stimulus-related signal increase were identified using an automated analysis program that computed for every pixel the difference between signal obtained during the 2.5 Hz (fastest

rate) stimulus periods and signal obtained during baseline periods preceding and following these cycles. Eight pixels from each temporal lobe showing the strongest responses were then analyzed quantitatively for rate effects. Data from each activation cycle were analyzed separately for each pixel. For each cycle of data, a local baseline was computed by averaging the eight signal values that immediately preceded and completed the cycle (Fig. 1). Four activation measurements were then made by computing the percent change difference between this baseline and the signals obtained during the last half of each 18-s activation period (Fig. 1). Analysis of the ten cycles in each condition thus yielded 40 activation measurements for each condition in each pixel. Repeated measures analysis of variance was used to assess the overall effects of (1) rate, (2) time from onset of activation stimuli (i.e., temporal position in the activation cycle), and (3) image series in which the measurement was acquired. The second of these variables enabled a measure of the short-term response 'decay' within each activation cycle, while the third variable provided a measure of response decrement over the entire test session.

Means and 95% confidence intervals were calculated for each rate condition in each of the eight pixels from each subject. An averaged rate-response function for each temporal lobe was derived by normalizing the standard deviation of activation measurements from each pixel and combining data across pixels and across subjects. These functions provide a general description, in arbitrary units, of the rate-response relationship for each hemisphere.

3. Results

Scores on the phoneme discrimination task showed high levels of accuracy at all presentation rates. No subject made more than 5% overall errors (misses + false alarms) in any condition, and d' scores were consistently very high across conditions (Table 3).

Increases in MRI signal that coincided with performance of the discrimination task were observed in the

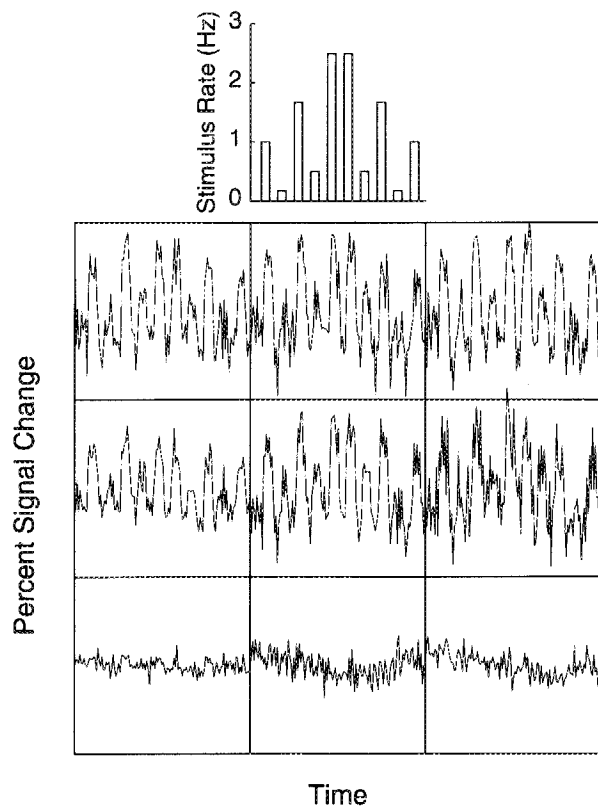


Fig. 2. MRI signal change over time in nine contiguous pixels of the left superior temporal gyrus of subject 1. The six pixels at the top of the array are active, while three pixels in the underlying white matter show no activity. The horizontal axis of each box in the array represents the total duration of an image series lasting 6 min 24 s and including ten activation periods. Vertical axes represent percent signal change and range from -5% to $+5\%$ relative to mean signal. The graph at the top of the figure illustrates the rate condition used in each of the ten activation cycles. Higher peaks in the signal data are associated with faster rate conditions.

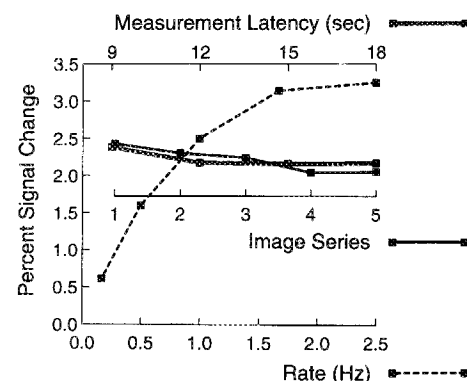


Fig. 3. Effects of three variables on percent signal change. Data points represent means computed across five subjects ($n > 3000$ per point). Measurement latency relative to stimulus onset, plotted against the upper x-axis in grey, produced a small decremental effect on percent change, with the largest effect noted between 9 and 12 seconds. The image series in which data were acquired, plotted in solid black against the middle x-axis, produced a somewhat larger decremental effect. The 5 image series were acquired over a 35 min test session. The rate at which stimuli were presented, plotted against the lower x-axis using a broken black line, produced the largest effects, accounting for 92.3% of the explained variance.

superior temporal lobe bilaterally in all subjects. Differences in fMRI response magnitude during different rate conditions were apparent on visual inspection of time-series data (Fig. 2). The 'temporal-spatial array' [1] of Fig. 2 shows signal change over time in 9 contiguous pixels of the left STG of subject 1. Taller peaks in the active pixels coincided with faster presentation rates.

One image series in one subject was discarded because of a scanner malfunction, resulting in a loss of 640 measurements, or 4% of the total data. Another 24 measurements (0.15%) were discarded because of head movement artifacts. Repeated measures ANOVA using the remaining 15,336 measurements pooled from all subjects confirmed a strong dependence of signal change on stimulus rate. Rate effects were highly significant ($F_{4,15236} = 1516$; $P < 0.0001$) and accounted for 92.3% of the explained variance. The image series (1–5) in which data were acquired had a small but

significant negative effect on signal change ($F_{3,15236} = 34$; $P < 0.0001$), indicating a modest response decrement over time during the 35 min test session (Fig. 3). This long-term decrement accounted for 2.1% of explained variance. A smaller, significant, negative effect of measurement latency (time from onset of stimuli to data acquisition) was also present ($F_{4,15236} = 18$; $P < 0.0001$), indicating a small response decrement occurring within each activation cycle (as suggested by the data sample of Fig. 1). This short-term decrement accounted for 0.8% of explained variance, while interactions between variables accounted in the aggregate for 4.8% of explained variance. Fig. 3 illustrates the relative magnitude and direction of rate, measurement latency, and image series effects on percent signal change.

Figs. 4–6 illustrate the location of the eight most active pixels from left and right temporal lobes of subjects 1–3, together with rate-response functions of

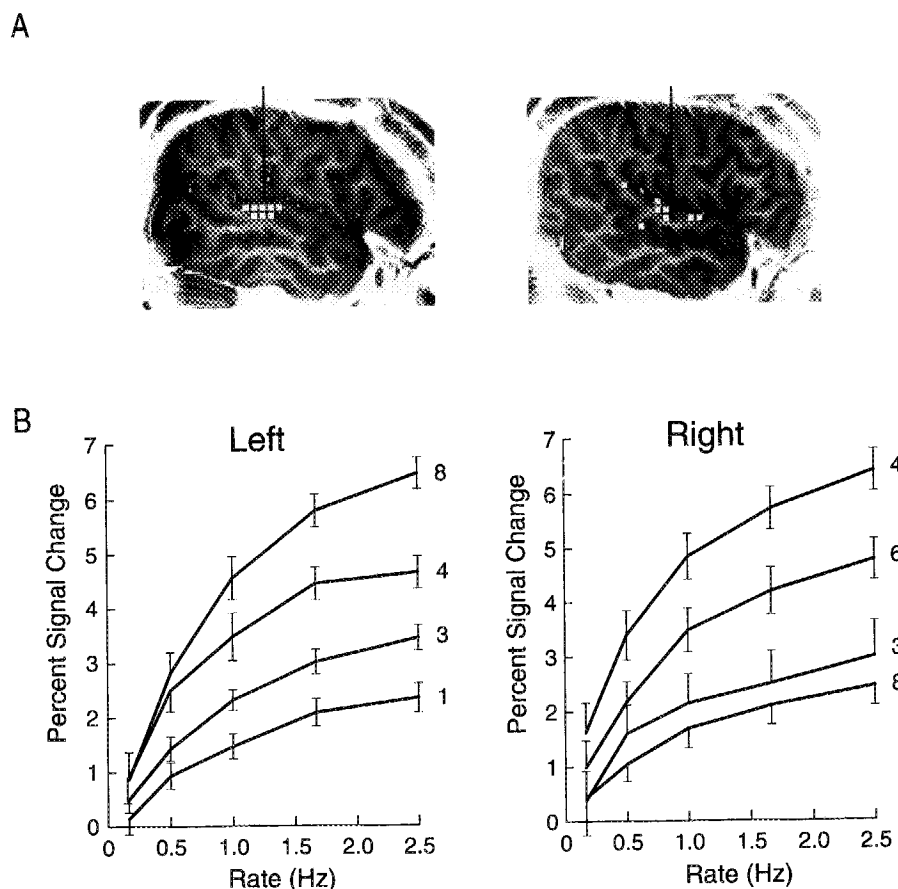


Fig. 4. A: location of strongest signal changes in left and right hemispheres of subject 1. Vertical lines indicate the most anterior transverse temporal sulcus, delineating the first Heschl's gyrus from the planum temporale. B: sample rate-response functions. Each point represents the mean of 40 percent change measurements made in each condition at each pixel location. Error bars indicate 95% confidence intervals. Numbers to the right of each response curve indicate the pixel marked in (A) from which the data were taken. Pixels marked in (A) are numbered sequentially from left to right, with those pixels forming columns ordered from top to bottom.

eight representative pixels. Vertical lines indicate the location of the transverse temporal sulcus. Error bars indicate 95% confidence intervals for each rate condition. Active pixels were located in Heschl's gyri and the transverse temporal sulcus, presumably near primary auditory cortex [11], in the lateral convex surface of the anterior superior temporal gyrus, in the planum polare (i.e., the dorsal superior temporal gyrus anterior to Heschl's gyrus), and occasionally in the planum temporale or the superior temporal sulcus. All of these pixels showed positive monotonic, non-linear relationships between stimulus rate and response magnitude over the range of rates studied. In most of the pixels an asymptotic effect is apparent as the rate increases, suggesting a monoexponential function underlying the rate-response relationship. Results from the other two subjects were similar. Fig. 7 illustrates average rate-response functions of the left and right temporal lobes, generated by combining normalized data from all subjects. Temporal lobe response functions were nearly identical in the two hemispheres.

4. Discussion

These data suggest that MRI signal changes reflecting brain tissue oxygenation in auditory cortex are dependent on stimulus presentation rate. Robust, highly significant rate effects were demonstrated by analysis of variance on combined subject data. Rate-response relations were nonlinear and monotonic over the range studied. These findings are in substantial accord with those obtained in the human visual system using PET and FMRI techniques [6,10], with some differences. It was previously proposed by Fox and Raichle [5] that the positive phase of the rate-response curve in visual cortex is linear, while our measurements show an apparent exponential decay with higher rates. Fig. 4 of Fox and Raichle suggests that there may have been a non-linear element to the positive phase of their response data as well, which was less apparent because of the sampling resolution within this rate range. Another feature of previous studies was the finding of a nonmonotonic (positive-then-negative) ef-

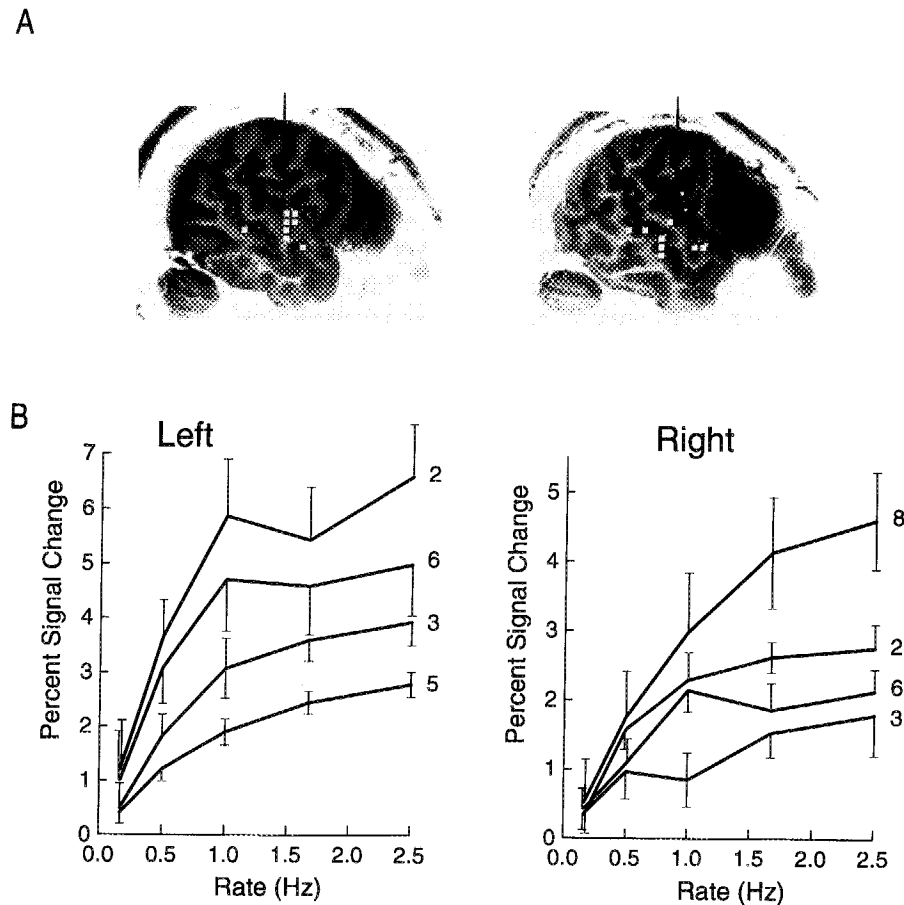
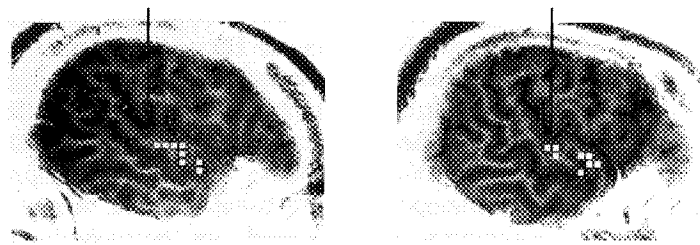


Fig. 5. Location of strongest signal changes and sample rate-response functions from subject 2. See Fig. 3 legend for details.

A



B

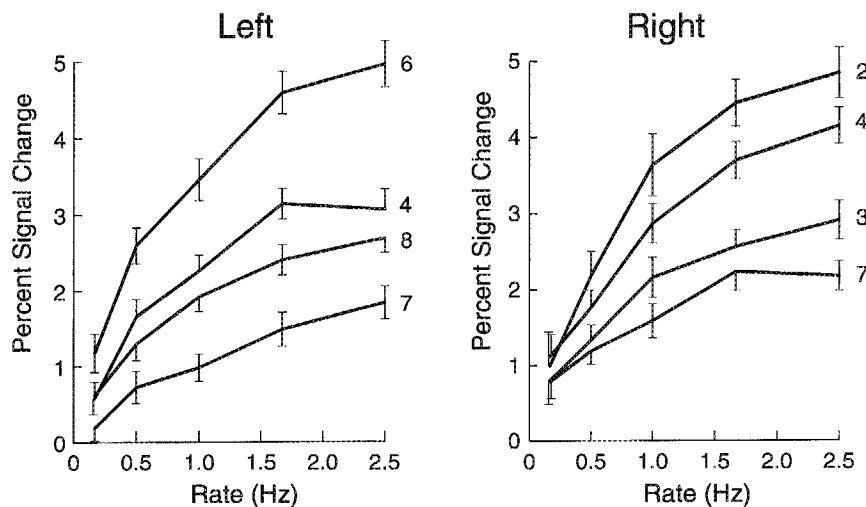


Fig. 6. Location of strongest signal changes and sample rate-response functions from subject 3. See Fig. 3 legend for details.

fect of increasing rate [5,6,10]. The more restricted range of rates available using CV stimuli may have precluded observation of such a negative effect in our study. Our results also share features with those of Price et al. [16], who examined superior temporal auditory responses at different word presentation rates using PET. The positive, monotonic rate-response

functions observed by Price et al. appeared to be linear in most instances, although the fastest rate used was 1.5 Hz.

Like PET, fMRI presumably reflects activity integrated over time within a large neuronal pool. If each presentation of a stimulus results in a similar set of neuronal events, then the integrated neuronal response, and the resulting blood flow response, will be a linear function of the number of stimuli presented per unit time [5]. Non-linear characteristics of the response function, such as those observed in this study, presumably reflect such factors as neuronal refractory periods, sense organ limitations, or non-linearities in the mechanism of blood flow regulation. Substantial electrophysiologic data regarding brainstem auditory evoked potentials [15,21] confirm that response magnitude in the lower auditory system is negatively affected by very high rates of stimulation. The auditory late response is a focal electrophysiologic phenomenon believed to reflect activity in neuronal populations of the superior temporal and parietal perisylvian cortex [20,26], and as such may represent an approximate electrical analogue of the oxygenation changes observed with fMRI in the present study. The magnitude of the auditory late

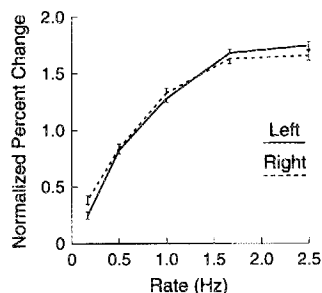


Fig. 7. Averaged rate-response functions for left and right temporal lobes generated by combining normalized data from all subjects. Each point represents the mean of some 1500 normalized percent change measurements (approximately 300 measurements in each rate condition in each hemisphere of each subject). Error bars indicate 95% confidence intervals for each rate condition.

response has been shown to exponentially decrease with increasing stimulus rates [4,13]. This negative effect, added to the positive integrative effect predicted with faster rates, might be expected to produce an exponential decay and eventual decrement of the FMRI response at higher rates. Our data are in good agreement with the first of these expectations.

Our findings suggest that FMRI may be a useful measure of regional oxygenation change in active brain tissue. More importantly, although FMRI presumably measures changes related to oxygenation in draining veins, the dependence of response magnitude on stimulation rate supports the hypothesis that the FMRI phenomenon indirectly reflects neuronal activity. Our results also suggest methods by which FMRI can be used to quantify response magnitude. FMRI is not presently capable of absolute measures of tissue oxygenation, and therefore is not ideal for comparisons between individuals. Our study demonstrates instead the usefulness of this technique for comparing distinct conditions within an individual. FMRI is particularly suitable for this application, since many contrasting stimulus conditions can be temporally juxtaposed within a short time interval. Significant differences in relative response magnitude can then be compared across conditions at a particular location in a given individual.

Several anatomic points require brief discussion. Our data are in agreement with recent evoked response and PET data showing bilateral, symmetric auditory cortex responses to speech stimuli [9,16,23]. Responses were localized to the superior temporal gyrus and superior temporal sulcus, similar to responses obtained in a previous FMRI study when subjects listened passively to speech sounds [3]. The data of Price et al. suggest an absence of rate dependence in the left posterior superior temporal gyrus [16], which the authors interpreted as evidence for higher level (i.e., time independent) processing in this region. In contrast to these data, we observed no areas that were free of rate effects. This could be explained by the 'nonsense' nature of our CV stimuli, from a failure to include such areas in the slice selection, or from other unknown factors.

Although we have used the term *rate* to describe differences between experimental conditions, the results presented here and in the study by Price et al. do not demonstrate a dependence of response on rate per se, since the total (integrated) stimulus *duration* also varied across conditions. This was a direct consequence of using stimuli of fixed duration, which resulted in a linear increase in total stimulus duration as rate was increased (Table 2). It will be important in future studies to independently assess rate and total duration using steady-state stimuli of variable duration. In examining responses to continuously variable stimuli such as speech, it will also be important to vary the *rate of*

change of formant transitions and other acoustic elements, and to quantify the temporal distribution of these elements across stimuli.

Data regarding the elementary stimulus variables determining cerebral blood flow responses have been relatively few. Information regarding auditory stimuli are particularly lacking given the large number of published cognitive language studies using functional imaging. Some of these experiments used fairly low presentation rates, which may have affected the results observed [8,19,23]. The findings reported here should prove useful as an initial guide in future investigations. As a general rule regarding speech stimuli, it seems advisable to use syllable presentation rates of at least 1.5 Hz to assure optimal stimulation of the superior temporal auditory cortex.

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